



## Antivirals, Influenza Therapeutic Class Review (TCR)

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## FDA-APPROVED INDICATIONS

Drug	Manufacturer	FDA-Approved Indications
oseltamivir (Tamiflu®) <sup>1</sup>	Genentech	<ul style="list-style-type: none"> <li>▪ Treatment of acute, uncomplicated illness due to influenza infection in patients 2 weeks of age and older who have been symptomatic for no more than 2 days</li> <li>▪ Prophylaxis of influenza in patients older than 1 year of age <ul style="list-style-type: none"> <li>– There is no evidence for efficacy of oseltamivir in any illness caused by agents other than influenza virus A and B.</li> <li>– Efficacy of oseltamivir in patients who begin treatment after more than 48 hours of symptoms has not been established.</li> </ul> </li> </ul>
rimantadine (Flumadine®) <sup>2</sup>	generic	<ul style="list-style-type: none"> <li>▪ Prophylaxis and treatment of illness caused by influenza A virus in adults (≥ 17 years older)</li> <li>▪ Prophylaxis of influenza A virus in patients older than 1 year of age (ages 1 to 16 years)</li> </ul>
zanamivir (Relenza®) <sup>3</sup>	GlaxoSmithKline	<ul style="list-style-type: none"> <li>▪ Treatment of uncomplicated acute illness due to influenza A or B virus in adults and pediatric patients 7 years and older who have been symptomatic for no more than 2 days</li> <li>▪ Prophylaxis of influenza in patients older than 5 years of age <ul style="list-style-type: none"> <li>– Not recommended for treatment or prophylaxis for influenza for patients with underlying airways diseases due to risk of bronchospasm</li> <li>– Not proven effective for treatment in patients with underlying airways diseases</li> <li>– Not proven effective for prophylaxis of influenza in nursing home residents</li> </ul> </li> </ul>

All antivirals for the treatment of influenza should be started as soon as possible and within 48 hours after illness onset to maximize the potential benefit of reducing duration of illness by one to two days.

Influenza viruses change over time. Emergence of drug resistance could decrease drug effectiveness. Prescribers should consider the most current available drug susceptibility information on influenza and treatment effects when deciding whether to use antiviral therapy.

Due to increased drug resistance to amantadine (Symmetrel®), this product is no longer reviewed here.

In December of 2014, peramivir (Rapivab™) was approved for the treatment of acute uncomplicated influenza in patients 18 years and older who have been symptomatic for no more than two days. Since the focus of the review is on oral medications and the peramivir is administered by intravenous infusion, it is not included in this review.

Antiviral treatment for influenza is not a substitute for annual vaccination for influenza.

## OVERVIEW

Influenza is a common illness affecting most people at least once in their lifetime. Influenza is most often self-limiting; however, very young, old, or immunocompromised patients are predisposed to secondary complications with potential fatalities. Symptoms include abrupt onset of fever, myalgia, headache, malaise, and respiratory signs and symptoms, including non-productive cough, sore throat, and rhinitis.<sup>4,5</sup> Children may also experience otitis media, nausea, and vomiting. Uncomplicated influenza illness typically resolves after three to seven days for most patients; however, cough and malaise can persist for more than two weeks.

### Vaccination

Influenza vaccination is the primary method for preventing influenza and the severe complications associated with influenza.<sup>6</sup> The Advisory Committee on Immunization Practices (ACIP) annual recommendation since 2010 has been an annual influenza vaccination for all people age six months and older at the beginning of flu season.<sup>7</sup> The Centers for Disease Control and Prevention (CDC) announced that the vaccine viral strain composition for the 2015–2016 influenza season would contain an A/California/7/2009 (H1N1) pdm09-like virus, an A/Switzerland/9715293/2013 (H3N2)-like virus, and a B/Phuket/3073/2013-like virus for trivalent vaccines. Quadrivalent vaccines also contain a B/Brisbane/60/2008-like virus.<sup>8</sup>

### Treatment

The CDC issued recommendations for the use of antivirals in the treatment and prevention of influenza for the 2015–2016 season that were not substantially different from the 2014–2015 season due to similar resistance patterns.<sup>9</sup>

Studies indicate that early antiviral treatment can reduce the risk of complications from influenza, such as pneumonia, respiratory failure, and death. Antiviral treatment is recommended as early as possible for any patient with confirmed or suspected influenza who has severe, complicated, or progressive illness; is hospitalized; or is at high risk for influenza complications. Patient groups at high risk for influenza complications include children younger than five years of age but especially children younger than two years of age; adults 65 years of age and older; women who are pregnant or post-partum (within two weeks after delivery); residents of nursing homes and other chronic-care facilities; American Indians and Alaskan Natives; and people with asthma; neurological and neurodevelopmental conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle, such as cerebral palsy, epilepsy, stroke, intellectual disability, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury); chronic lung disease (such as chronic obstructive pulmonary disease and cystic fibrosis); heart disease (such as congenital heart disease, congestive heart failure and coronary artery disease); blood disorders (such as sickle cell disease); endocrine disorders (such as diabetes mellitus); kidney disorders; liver disorder; metabolic disorders (such as inherited metabolic disorders and mitochondrial disorders); weakened immune system due to disease or medication (such as people with HIV or AIDS, or cancer or those on chronic steroids); people younger than 19 years of age who are receiving long-term aspirin therapy and people who are morbidly obese (Body Mass Index of 40 or greater).<sup>10</sup> Clinical judgment, based on the patient's disease severity and progression, age, underlying medical conditions, likelihood of influenza, and time since onset of symptoms, is important to consider when making antiviral treatment decisions for high-risk outpatients.

When indicated, antiviral treatment should be started as soon as possible after illness onset. Studies show that treatment initiated early (e.g., within 48 hours of illness onset) is more likely to provide benefit. Treatment should not wait for laboratory confirmation of influenza because a negative rapid test for influenza does not rule out influenza. Treatment with oseltamivir (Tamiflu) or zanamivir (Relenza) is recommended for all people with suspected or confirmed influenza according to approved ages and dosages. Antiviral treatment also can be considered for any previously healthy, non-high-risk, symptomatic outpatient with confirmed or suspected influenza based upon clinical judgment, if treatment can be initiated within 48 hours of illness onset.

## Prophylaxis

According to the CDC antiviral medications are about 70% to 90% effective in preventing influenza and are useful adjuncts to influenza vaccination, but that annual influenza vaccination alone is the best way to prevent influenza. Because of the possibility of emergence of antiviral resistance viruses, widespread or routine use of antiviral medications for chemoprophylaxis is not recommended.<sup>11</sup>

Antiviral chemoprophylaxis generally should be reserved for people at higher risk for influenza-related complications who have had contact with someone likely to have been infected with influenza.<sup>12</sup> The infectious period for influenza is defined as one day before until 24 hours after fever ends. Children can shed influenza viruses for longer periods. Antivirals are not generally recommended if more than 48 hours have elapsed since the last contact with an infectious person. Antiviral chemoprophylaxis is not appropriate for healthy children or adults based on potential exposure in the community. Influenza vaccination should be the primary method of prevention, when possible, rather than chemoprophylaxis with antiviral medications.

An emphasis on early treatment and monitoring is an alternative to chemoprophylaxis after a suspected exposure for some people. Prophylaxis may be considered for the following patient groups: people at high risk of influenza complications during the first two weeks following vaccination after exposure to an infectious person; people with severe immune deficiencies or others who might not respond to influenza vaccination, such as people receiving immunosuppressive medications, after exposure to an infectious person; people at high risk for complications from influenza who cannot receive influenza vaccine due to a contraindication after exposure to an infectious person; and residents of institutions, such as long-term care facilities, during influenza outbreaks in the institution.

## PHARMACOLOGY

Drug Mechanism of Action	Mechanism of Action
oseltamivir (Tamiflu) <sup>13</sup>	<ul style="list-style-type: none"> <li>Oseltamivir is a prodrug that is converted to the active form, oseltamivir carboxylate. It inhibits influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release. Oseltamivir is active against influenza A and B viruses.</li> </ul>
rimantadine (Flumadine) <sup>14</sup>	<ul style="list-style-type: none"> <li>Rimantadine appears to exert its inhibitory effect early in the viral replication cycle, possibly inhibiting the uncoating of the virus.</li> <li>It is active against the influenza A virus, but not influenza B.</li> </ul>
zanamivir (Relenza) <sup>15</sup>	<ul style="list-style-type: none"> <li>Zanamivir inhibits influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release. Zanamivir is active against influenza A and B viruses.</li> </ul>

### Viral Resistance

Influenza viral resistance has been documented following treatment with zanamivir and oseltamivir.<sup>16,17</sup> *In vitro* viral cross-resistance between oseltamivir (Tamiflu) and zanamivir (Relenza) has been identified; however, the incidence and extent of clinical cross-resistance is difficult to determine.

High levels of resistance (93%) of influenza A virus to amantadine and rimantadine were observed in the U.S. in 2005-2006 and these levels have persisted among viruses currently circulating.<sup>18,19</sup> The CDC monitors viral resistance and responds to changes in resistance by publishing recommendations based on the incidence of viral resistance.<sup>20</sup> Due to high levels of resistance, amantadine and rimantadine are not recommended.<sup>21</sup>

Rare, sporadic cases of oseltamivir-resistant 2009 (H1N1) and influenza A (H3N2) viruses have been detected worldwide, but the majority of the viruses are susceptible and oseltamivir is still recommended.<sup>22</sup> The mutation of these viruses shows the H275Y mutation that confers resistance to the antiviral oseltamivir, but not to the antiviral zanamivir. According to WHO, the risk of viral resistance is considered higher in patients with severely compromised or suppressed immune systems who have prolonged illness, have received oseltamivir treatment (especially for an extended duration), but still have evidence of persistent viral replication.<sup>23</sup> The risk of resistance is also considered higher in people who receive oseltamivir for post-exposure prophylaxis and who then develop illness despite taking oseltamivir. No evidence exists that oseltamivir-resistant viruses are causing different or more severe forms of illness. Since October 1 2015, a total of 647 influenza specimens have been tested to determine antiviral resistance. The 528 influenza A (H3N2) and influenza B isolates have been 100% susceptible to oseltamivir, zanamivir, and peramivir. Of the influenza A (H1N1) pdm09 isolates, 1 out of 40 samples tested demonstrated resistance to oseltamivir, while there was 100% susceptibility to zanamivir and peramivir. Due to consistent high levels of resistance, rimantadine is no longer tested by the CDC for resistance levels.<sup>24</sup>

### Susceptibilities as of October 1, 2015 according to CDC<sup>25</sup>

Influenza type	oseltamivir	zanamivir
Influenza A (H3N2)	Susceptible	Susceptible
Influenza B	Susceptible	Susceptible
Influenza A (H1N1) pdm09	Susceptible	Susceptible

## PHARMACOKINETICS

Drug	Bioavailability (%)	Half-Life (hr)	Metabolism	Excretion
oseltamivir (Tamiflu) <sup>26</sup>	75	1–3 (parent); 6–10 (metabolite)	1 active – oseltamivir carboxylate	Predominantly renal
rimantadine (Flumadine) <sup>27</sup>	--	13–65	At least 4 metabolites	Hepatically metabolized, metabolites renally excreted
zanamivir (Relenza) <sup>28</sup>	4–17	2.5–5.1	No metabolites	Renally excreted

## CONTRAINDICATIONS/WARNINGS

Cross-hypersensitivity between rimantadine is possible and is a contraindication for use.<sup>29</sup>

Rimantadine has been associated with an increase in seizure activity for patients who have a history of seizure activity.<sup>30</sup> Patients with renal or hepatic insufficiency should be closely observed for signs of adverse effects when taking rimantadine due to an accumulation of the parent drug and its metabolites. Transmission of rimantadine resistant virus should be considered when treating patients whose contacts are at high risk for influenza A illness. Influenza A virus strains resistant to rimantadine can emerge during treatment, and such resistant strains have been shown to be transmissible and to cause typical influenza illness. Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. Rimantadine has not been shown to prevent such complications.

Zanamivir (Relenza) should not be used in patients with a history of allergic reaction to any component of zanamivir including lactose (contains milk proteins).<sup>31</sup> Zanamivir is not recommended for treatment or prophylaxis of influenza in individuals with underlying airway diseases such as asthma or chronic obstructive pulmonary disease due to risk of serious bronchospasm. Zanamivir should be discontinued in any patient who develops bronchospasm or respiratory difficulty. Effectiveness of prophylaxis of influenza in the nursing home setting has not been established. Allergic-like reactions, including oropharyngeal edema, serious skin rashes, and anaphylaxis have been reported in post-marketing experience with zanamivir. There is no evidence for efficacy of zanamivir in an illness caused by infectious agents other than influenza A or B. Patients should be advised that the use of zanamivir for the treatment of influenza has not been shown to reduce the risk of transmission of influenza to others nor has zanamivir been proven to prevent serious complications, including serious bacterial infections. Zanamivir must not be made into an extemporaneous solution for administration by nebulization or mechanical ventilation. Zanamivir inhalation powder must only be administered using the device provided.

Oseltamivir (Tamiflu) is contraindicated in patients with known serious hypersensitivity to oseltamivir or any component of the product. Severe allergic reactions have included anaphylaxis and serious skin reactions, including toxic epidermal necrolysis, Stevens-Johnson Syndrome, and erythema multiforme. Efficacy of oseltamivir in the treatment of influenza has not been established in patients with chronic cardiac disease and/or respiratory disease.<sup>32</sup> No difference in the incidence of complications was observed between the treatment and placebo groups in this population. No information is available regarding treatment of influenza in patients with any medical condition sufficiently severe or unstable

to be considered at imminent risk of requiring hospitalization. Efficacy of oseltamivir for treatment or prophylaxis of influenza has not been established in immunocompromised patients. Serious bacterial infections may begin with influenza-like symptoms or may co-exist or occur as complications during the course of influenza. Oseltamivir has not been shown to prevent these complications.

## Neuropsychiatric Reactions<sup>33,34</sup>

Hallucinations, delirium, and abnormal behavior have been reported with influenza infection. Neuropsychiatric reactions have been noted in post-marketing surveillance of oseltamivir and zanamivir. Reports including those with fatal outcomes have described self-injury and delirium in mostly pediatric patients on oseltamivir or zanamivir with influenza. Event reports in pediatric patients have noted abrupt onset and rapid resolution of neuropsychiatric events. Unusual behavior should be reported to a healthcare professional promptly. If neuropsychiatric events occur, the risks and benefits of continuing treatment should be evaluated.

## Drug Interactions<sup>35,36,37</sup>

Administration of agents in this class with Influenza Virus Vaccine Live (FluMist®) has not been evaluated. Because of the potential interference between the antivirals and FluMist, it is advisable that FluMist not be administered until 48 hours after cessation of anti-influenza antiviral therapy. Anti-influenza antivirals should not be administered until two weeks after the FluMist vaccine administration unless medically necessary. Trivalent inactivated influenza vaccine can be administered at any time relative to use of drugs in this category.

No other drug interactions are expected with zanamivir or oseltamivir.

## ADVERSE EFFECTS

Drug	Headache	Nausea	Dizziness	Abd. Pain	Vomiting	Diarrhea
oseltamivir (Tamiflu) <sup>38</sup> 75 mg twice daily n=724 adults; placebo n=716	2 (2)	10 (6)	2 (3)	2 (2)	9 (3)	7 (10)
rimantadine (Flumadine) <sup>39</sup> n=1,027	1.4 (1.3)	2.8 (1.6)	1.9 (1.1)	1.4 (0.8)	1.7 (0.6)	0.3-1
zanamivir (Relenza) <sup>40</sup> 10 mg twice daily n=1,132 adults; placebo n=1,520	2 (3)	3 (3)	2 (<1)	<1.5	1 (2)	3 (4)

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

In the treatment of influenza, vomiting was the most common adverse effect in children receiving oseltamivir (15% versus 9% in the placebo group).<sup>41</sup> Vomiting is also the most common adverse event in children undergoing prophylaxis for influenza with oseltamivir. Oseltamivir may be administered with or without food; however, drug tolerability may be increased for certain patients if taken with food.<sup>42</sup>

The most common adverse effect in children receiving zanamivir was ear, nose, and throat infections. These occurred at a rate of 5% for both zanamivir-treated and placebo-treated patients.<sup>43</sup>

## **SPECIAL POPULATIONS**<sup>44,45,46</sup>

### **Pediatrics**

Rimantadine is indicated for the prophylaxis of influenza A infections in children ages one year to 16 years old; however, treatment with rimantadine is limited to patients 17 years of age and older.

Early empiric treatment with oseltamivir (Tamiflu) or zanamivir (Relenza) should be considered for people with suspected or confirmed influenza who require hospitalization and/or have progressive, severe, or complicated illness, regardless of previous health status, and/or with risk factors for severe illness.<sup>47</sup> The risk factors for severe illness, according to the CDC, are the same medical conditions in adults and in children. Children less than five years of age are at higher risk for complications secondary to influenza, especially children less than two years of age. According to the American Academy of Pediatrics 2015–2016 recommendations for prevention and control of influenza in children, children at higher risk for complications related to influenza infection include those with neurological disorders, chronic respiratory diseases, moderate to profound intellectual disability or developmental delay, deficiencies in immune function or conditions which require medications or treatments that result in significant immune deficiencies, sickle cell anemia and other hemoglobinopathies, hemodynamically significant heart disease, asthma or other chronic pulmonary diseases including cystic fibrosis, conditions that can compromise respiratory function or handling of secretions or can increase the risk of aspiration, chronic renal dysfunction, long-term aspirin therapy including juvenile idiopathic arthritis or Kawasaki disease, or significant metabolic disorders including diabetes mellitus.<sup>48</sup>

Oseltamivir has been approved for treatment of influenza in children two weeks of age and older and for prevention of influenza in children one year of age and older. Zanamivir has been approved for prevention of influenza in children as young as five years and is approved for the treatment of influenza for children ages seven years and older. The limitation of zanamivir is the dose administration technique of the inhaler.

### **oseltamivir (Tamiflu) versus placebo in children**

Oseltamivir was studied in a randomized, double-blind, placebo-controlled trial with 695 children ages one to 12 years with fever and history of cough or coryza of less than 48 hours of duration.<sup>49</sup> Patients were randomized to oseltamivir 2 mg/kg twice daily or placebo for five days. Sixty-five percent of children (n=465) were found to have influenza. Oseltamivir reduced the median duration of illness by 36 hours (26%) in the influenza-infected children compared to placebo (101 hours versus 137 hours, p<0.0001). Oseltamivir reduced cough, coryza, and duration of fever. New diagnoses of acute otitis media were also reduced in the oseltamivir group (12 versus 21%, respectively). Use of antibiotics was significantly lower in the influenza-infected oseltamivir group compared to the influenza-infected placebo group (31 versus 41%, respectively, p=0.03). Oseltamivir group experienced more emesis than placebo group.

In a randomized, double-blind, placebo-controlled study, the efficacy of oseltamivir initiated within 24 hours of symptom onset in 408 children ages one to three years was evaluated.<sup>50</sup> Patients (n=98) had

laboratory-confirmed influenza during the 2007-2008 or 2008-2009 influenza seasons in Finland. Patients received oseltamivir suspension or placebo twice daily for five days. For the patients initiating oseltamivir within 12 hours of symptom onset (secondary outcome measure), oseltamivir decreased the incidence of acute otitis media (AOM) by 85% (95% CI, 25-97). No significant reduction in AOM was observed in the group of patients who initiated therapy within 24 hours of symptom onset, the primary endpoint. For patients with influenza A (n=79), oseltamivir initiated within 24 hours of symptom onset shortened the median time to resolution of illness by 3.5 days (three days versus 6.5 days; p=0.006) in all children and by four days (3.4 days versus 7.3 days; p=0.006) in unvaccinated children. Efficacy was not demonstrated against influenza B infections (n=19).

### **zanamivir (Relenza) versus placebo in children**

A double-blind, randomized, placebo-controlled, parallel-group, multicenter study enrolled children, five to 12 years of age, with influenza-like symptoms for no more than 36 hours.<sup>51</sup> Patients were randomized to zanamivir 10 mg twice daily or placebo for five days. Symptoms were recorded on diary cards twice daily during treatment, nine days after treatment, and potentially an additional 14 days, if symptoms persisted. Of the 471 children enrolled in the study, 346 (73%) patients were influenza-positive by culture, serology, or polymerase chain reaction. Of those with confirmed infection, 65% had influenza A and 35% had influenza B. Zanamivir reduced the median time to symptom alleviation by 1.25 days compared with placebo among patients with confirmed influenza infection (p<0.001). Zanamivir-treated patients returned to normal activities significantly faster and took significantly fewer relief medications than placebo-treated patients. Zanamivir was well-tolerated.

### **Pregnancy**

All agents in this class are Pregnancy Category C.

Pregnant women are at a higher risk for severe complications and death from influenza. In the current 2011 recommendations from the CDC, treatment with oseltamivir or zanamivir is recommended for pregnant women or women who are up to two weeks postpartum (including following pregnancy loss) with suspected or confirmed influenza.<sup>52</sup> Treatment can be given during any trimester of pregnancy. Oseltamivir is preferred for treatment of pregnant women. Zanamivir might be preferred by some providers because of its limited systemic absorption; however, respiratory complications that might be associated with zanamivir because of its inhaled route of administration need to be considered, especially in women at risk for respiratory problems.

### **Geriatrics**

Rimantadine elimination is reduced in patients over age 64 years. An increase in central nervous system and gastrointestinal adverse effects are seen at the standard doses in geriatric patients receiving 200 or 400 mg of rimantadine. Dosage adjustments are listed in the Dosages section.

No dosage adjustment is required for oseltamivir or zanamivir in the geriatric population.

### **Renal Impairment**

Oseltamivir dose and/or interval should be reduced in patients with an estimated creatinine clearance of 10-60 mL/minute or in patients with endstage renal disease (ESRD).

## DOSAGES

Drug/ Dosage Forms	Treatment of influenza		Prophylaxis of influenza	
	Adults	Pediatrics	Adults	Pediatrics
oseltamivir (Tamiflu) <sup>53</sup> 30, 45, 75 mg capsules; 6 mg/1 mL oral suspension	75 mg twice daily for 5 days (≥13 years) Initiate therapy within 2 days of onset of symptoms.	2 weeks to 1 year: 3mg/kg twice daily >1 to <13 years: < 15 kg: 30 mg twice daily; 15-23 kg: 45 mg twice daily; 23-40 kg: 60 mg twice daily; > 40 kg: 75 mg twice daily	75 mg daily for 10 days (≥13 years) Initiate therapy within 2 days of exposure.	>1 to < 13 years: < 15 kg: 30 mg daily for 10 days; 15-23 kg: 45 mg daily for 10 days; 23-40 kg: 60 mg daily for 10 days; > 40 kg: 75 mg daily for 10 days May give for up to 6 weeks for community outbreak.
rimantadine (Flumadine) <sup>54</sup> 100 mg tablet	For Influenza A only 100 mg twice daily for 7 days (≥17 years)	--	100 mg twice daily (≥17 years)	1 to 9 years: 5 mg/kg daily up to 150 mg daily For 10 to 16 years of age, use adult dosage
zanamivir (Relenza) <sup>55</sup> 5 mg diskhaler	Two inhalations (10 mg) twice daily for 5 days Initiate therapy within 2 days of onset of symptoms.	≥7 years: Two inhalations (10 mg) twice daily for 5 days	2 inhalations (10 mg) once daily for 10 days (household setting) or 28 days (community outbreaks)	≥5 years: 2 inhalations (10 mg) once daily for 10 days (household setting) or 28 days (community outbreaks)

Patients scheduled to use an inhaled bronchodilator at the same time as zanamivir should use their bronchodilator before taking zanamivir.

## DOSAGE ADJUSTMENTS

Drug/ Dosage Forms	Treatment of influenza		Prophylaxis of influenza	
	Disease state/concurrent condition	Recommended dosage adjustment	Disease state/concurrent condition	Recommended dosage adjustment
oseltamivir (Tamiflu) <sup>56</sup>	Renal impairment Moderate: CrCL >30-60 mL/min  Severe: CrCL >10-30 mL/min  ESRD (hemodialysis): CrCL ≤10 mL/min  ESRD (CAPD): CrCL ≤10 mL/min	30 mg twice daily for 5 days  30 mg once daily for 5 days  30 mg after hemodialysis cycles not to exceed 5 days  30 mg immediately after a dialysis exchange	Renal impairment Moderate: CrCL >30-60 mL/min  Severe: CrCL >10-30 mL/min  ESRD (hemodialysis): CrCL ≤10 mL/min  ESRD (CAPD): CrCL ≤10 mL/min	30 mg once daily  30 mg every other day  30 mg after alternate hemodialysis cycles  30 mg once weekly after dialysis exchange
rimantadine <sup>57</sup>	Severe hepatic dysfunction Renal insufficiency (CrCl 5 to 29 mL/min) Renal failure (CrCl ≤10 mL/min) Elderly nursing home patients	100 mg daily	Severe hepatic dysfunction Renal insufficiency (CrCl 5 to 29 mL/min) Renal failure (CrCl ≤10 mL/min) Elderly nursing home patients	100 mg daily
zanamivir (Relenza) <sup>58</sup>	Not recommended for patients with airway diseases such as chronic obstructive pulmonary disease and asthma			

CrCl = creatinine clearance; ESRD = end stage renal disease; CAPD = continuous ambulatory peritoneal dialysis

## CLINICAL TRIALS

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled trials performed in the United States comparing oral and inhaled agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Due to changes in resistance and practice patterns over time, studies conducted more than fifteen years ago were excluded. Because of the paucity of active controlled trials of the antiviral agents used for treatment and prophylaxis of influenza, studies that were placebo-controlled, randomized trials in humans using antiviral agents for the treatment or prevention of influenza were included. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this

therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

## **Influenza – Treatment**

### ***oseltamivir (Tamiflu) versus placebo***

A randomized, double-blind study was performed in 629 healthy nonimmunized adults in the United States with febrile illness of less than 36 hours duration.<sup>59</sup> Patients were randomized to receive oseltamivir 75 mg or 150 mg or matching placebo twice daily. In the 374 patients infected with influenza, median duration of illness was shorter in the oseltamivir 75 mg (71.5 hours;  $p < 0.001$  versus placebo) and 150 mg groups (69.9 hours;  $p = 0.006$  versus placebo) compared to placebo (103.3 hours). There was no difference observed between the two active treatment regimens. Secondary complications, such as bronchitis and sinusitis, occurred more frequently in the placebo group (15%) than the oseltamivir groups (7%;  $p = 0.03$ ). Additionally, oseltamivir-treated patients returned to usual activities two to three days earlier than placebo-treated patients ( $p \leq 0.05$ ). Nausea and vomiting occurred more frequently in the oseltamivir groups (combined incidence of 18 and 14.1%, respectively;  $p = 0.002$ ) compared to placebo (7.4 and 3.4%;  $p < 0.001$ ).

A randomized, double-blind, controlled trial was conducted in 726 previously healthy nonimmunized adults with febrile influenza-like illness of up to 36 hours duration.<sup>60</sup> Patients were assigned to oseltamivir 75 mg, oseltamivir 150 mg, or placebo twice daily for five days. Infection was confirmed in 66% of patients. Compared to placebo (median duration 116.5 hours), the duration of illness, the primary endpoint, was 29 hours shorter in the oseltamivir 75 mg group (median duration 87.4 hours;  $p = 0.02$ ) and 35 hours shorter in the oseltamivir 150 mg group (median duration 81.8 hours;  $p = 0.01$ ). The effect of oseltamivir was apparent within 24 hours of the start of treatment. In patients treated within 24 hours of symptom onset, symptoms were alleviated in 74.5 hours in the oseltamivir 75 mg group, in 70.7 hours in the oseltamivir 150 mg group and in 117.5 hours in the placebo group ( $p \leq 0.02$  for both active treatments compared to placebo). Oseltamivir was associated with lower symptom scores, less viral shedding, and improved health, activity, and sleep quality. Oseltamivir was well tolerated.

### ***zanamivir (Relenza) versus placebo***

In a double-blind trial, 27 otherwise healthy adult patients were randomized to zanamivir 10 mg twice daily for five days or matching placebo.<sup>61</sup> Treatment was started within the first or second day of a flu-like illness. After 12 hours of treatment (e.g., one dose), median virus titers changed by  $-1.0 \log_{10}$  TCID<sub>50</sub>/mL in the zanamivir group compared with  $+0.42 \log_{10}$  change in the placebo group ( $p = 0.08$ ). This was associated with a 4.5 day (47.4%) reduction in the median time to alleviation of all significant flu symptoms in the zanamivir recipients ( $p = 0.03$  after adjusting for the initial virus titer and the time between onset of symptoms and treatment). Resistance to zanamivir was not detected in virus isolates.

In a randomized, double-blind trial, 356 patients aged 12 years and older were recruited within two days of onset of typical influenza symptoms.<sup>62</sup> Patients were randomized to receive inhaled zanamivir 10 mg twice daily for five days or matching placebo. Influenza was laboratory-confirmed in 277 (78%)

of the patients; 32 (9%) patients were considered high-risk (elderly or with underlying medical conditions). The primary endpoint, time to alleviation of clinically significant symptoms of influenza, was significantly reduced by zanamivir compared to placebo (5 and 7.5 days, respectively;  $p < 0.001$ ). Zanamivir was well tolerated.

### ***oseltamivir (Tamiflu) and zanamivir (Relenza)***

Although the study was conducted in an open-label manner, it has been included due to a lack of other direct comparative data. In a Japanese study, the effectiveness of zanamivir with oseltamivir for influenza A and B were compared in 1,113 patients during the 2006-2007 influenza season.<sup>63</sup> The duration of fever ( $\geq 37.5^{\circ}\text{C}$ ) after the first dose was less with zanamivir (31.8 hrs) compared to oseltamivir (35.5 hours;  $p < 0.05$ ) in patients with influenza A. For patients with influenza B, fever duration after starting zanamivir therapy (35.8 hrs) was significantly shorter than that of oseltamivir (52.7 hrs;  $p < 0.001$ ). By multiple regression analysis, therapy (zanamivir or oseltamivir) was the major determinant affecting the duration of fever for influenza B.

## **Influenza – Prophylaxis**

### ***oseltamivir (Tamiflu) versus placebo***

A study compared the efficacy of oseltamivir in prevention of household contacts acquiring influenza from the index case. A total of 955 household contacts of people with influenza were enrolled in a preventative, double-blind study and randomized to oseltamivir 75 mg once daily or placebo for seven days.<sup>64</sup> Randomization occurred by household within 48 hours of symptom onset of the index case of influenza. The index case patients did not receive therapy in the study. The overall protective efficacy of oseltamivir against clinical influenza was 89% for individuals (95% confidence interval [CI], 67-97%;  $p < 0.001$ ) and 84% for households (95% CI, 49-95%;  $p < 0.001$ ). Gastrointestinal adverse events were similar in both groups (oseltamivir, 9.3%; placebo, 7.2%).

In a double-blind, placebo-controlled, parallel-group, multicenter study, 548 frail, elderly nursing home occupants (mean age 81 years,  $>80\%$  vaccinated for influenza) were randomized to prophylaxis with oseltamivir 75 mg or placebo once daily for six weeks, beginning when influenza was detected locally.<sup>65</sup> The administration of oseltamivir resulted in a 92% reduction in the incidence of laboratory-confirmed clinical influenza compared with placebo (0.4 and 4.4%, respectively;  $p = 0.002$ ). In vaccinated subjects, influenza was confirmed in 0.5% of oseltamivir patients and 5% of patients randomized to placebo ( $p = 0.003$ ). Oseltamivir use was also associated with a significant reduction in the incidence of secondary complications (0.4% versus 2.6% for placebo;  $p = 0.037$ ). Oseltamivir was well tolerated with a similar incidence of adverse events, including gastrointestinal effects, occurring in both groups.

### ***zanamivir (Relenza) versus placebo***

Prior to influenza season, 799 families with two to five members and at least one child who was five years of age or older were enrolled in a double-blind, placebo-controlled study.<sup>66</sup> If an influenza-like illness developed in one member, all family members aged five years and older were randomly assigned to receive either inhaled zanamivir or placebo. The family member with the index illness was treated with either zanamivir or placebo twice daily for five days, and the other family members received either zanamivir or placebo once daily as prophylaxis for ten days. The proportion of families with at least one initially healthy household contact in whom influenza developed (the primary

endpoint) was significantly lower in the zanamivir group than in the placebo group (4 versus 19%;  $p<0.001$ ). Zanamivir provided protection against both influenza A and influenza B. Among the subjects with index cases of laboratory-confirmed influenza, the median duration of symptoms was 2.5 days shorter in the zanamivir group than in the placebo group (5 versus 7.5 days;  $p=0.01$ ). Viral resistance to zanamivir was not identified in this study. Zanamivir was well tolerated.

After close contacts with index cases of influenza-like illnesses, 575 subjects were randomized to receive one of four prophylactic regimens in a double-blind manner: placebo, intranasal zanamivir, inhaled zanamivir and inhaled plus intranasal zanamivir, each given for five days.<sup>67</sup> Of 25 subjects (4%) who developed symptomatic influenza during the five days of prophylaxis, nine (36%) were in the placebo group, eight (32%) were in the intranasal zanamivir group, three (12%) were in the inhaled zanamivir group, and five (20%) were in the inhaled plus intranasal zanamivir group ( $p=NS$  for all comparisons to placebo).

A double-blind, randomized study evaluated inhaled zanamivir for the prevention of influenza in families.<sup>68</sup> Once a person with a suspected case of influenza was identified (index patient), treatment of all other household members (contacts) five years and older was initiated. Contacts received either 10 mg zanamivir or placebo inhaled once daily for ten days. Index cases were not treated with antivirals in the trial. In total, 487 households were enrolled with 1,291 contacts randomly assigned to receive prophylaxis. Four percent of zanamivir versus 19% of placebo households had at least one contact who developed symptomatic, laboratory-confirmed influenza, representing 81% protective efficacy (95% CI, 64 to 90%,  $p<0.001$ ). In the intent-to-treat population, contacts with laboratory-confirmed influenza were significantly lower in the zanamivir group (7 and 17% for the zanamivir and placebo groups, respectively; 59% protective efficacy; 95% CI, 44 to 70,  $p<0.001$ ). Protective efficacy was also high for individuals (82%) and against both influenza types A and B (78 and 85%, respectively, for households). Zanamivir was well tolerated.

In a multicenter, randomized, double-blind, placebo-controlled, parallel-group study, the efficacy and safety of zanamivir for the prevention of influenza in community-dwelling patients who were at high risk for developing complications of influenza were evaluated.<sup>69</sup> The study was conducted in the 2000-2001 influenza season. To be enrolled, patients were able to use the Diskhaler device and were able to take the first dose of study medication within five days of laboratory-confirmed local influenza activity. Patients ( $n=3,363$ ) were randomized to receive inhaled zanamivir 10 mg or placebo once daily for 28 days. The proportion of randomized subjects who developed symptomatic influenza during prophylaxis was significantly lower in those patients receiving zanamivir (4/1,678 versus 23/1,685; relative risk 0.17; [95% CI, 0.07 to 0.44,  $p<0.001$ ]). Zanamivir provided a protective efficacy of 83%. Significantly fewer complications were observed in the zanamivir-treated patients (1/1,678 versus 8/1,685; relative risk 0.12 [95% CI, 0.002 to 0.73;  $p=0.042$ ]). Influenza-like illness was reported in 9% in the zanamivir-treated patients and 10% in the placebo-treated patients. Adverse effects were similar between the groups with the most common reports being headache, cough, and throat and tonsil discomfort/pain. The incidences of viral respiratory infections or ear, nose, and throat infections were similar between the two groups. No resistance to zanamivir was identified in the study.

## META-ANALYSES

### rimantadine<sup>70,71,72,73</sup>

The use of rimantadine for the treatment of influenza is based on two systematic reviews. The first review included three placebo-controlled trials of rimantadine in adults and the second review included one placebo-controlled trial of rimantadine in children. Rimantadine is superior to placebo, with a reduction in duration of fever for adults of greater than one day (MD=-1.24; 95% CI: -1.71 to -0.76) and fewer cases of fever in children. No statistically significant difference was demonstrated between rimantadine and placebo in the occurrence of adverse events.

### Adults

A 2006 meta-analysis evaluated the prevention and treatment efficacy in symptomatic and asymptomatic influenza in healthy adults.<sup>74</sup> Rimantadine had fewer data but similar effects. In symptomatic influenza, efficacy rates of oseltamivir 75 mg and 150 mg daily were 61 and 73%, respectively, whereas zanamivir was 62%. For post-exposure prevention, oseltamivir was associated with 58.5% reduction within households and 68 to 89% for contacts of index cases. Symptom duration was shorter by one to two days with both oseltamivir and zanamivir when therapy was started within 36 to 48 hours of onset.<sup>75</sup> Oseltamivir was associated with nausea. Both oseltamivir and zanamivir reduced nasal viral shedding; however, amantadine did not. In asymptomatic influenza, antivirals had no effect. Another 2003 meta-analysis found that oseltamivir was associated with a reduction in lower respiratory tract complications, antibiotic use, and hospitalizations related to influenza in both healthy and at risk patients.<sup>76</sup>

A 2009 systematic review included randomized placebo controlled studies of neuraminidase inhibitors in otherwise healthy adults exposed to naturally occurring influenza.<sup>77,78</sup> A total of 20 trials were included. In the four trials evaluating prophylaxis, the neuraminidase inhibitors had no effect against influenza-like illness or asymptomatic influenza. The efficacy of oseltamivir 75 mg daily against symptomatic laboratory confirmed influenza was 61% (risk ratio 0.39; 95% CI, 0.18 to 0.85). Inhaled zanamivir 10 mg daily was 62% efficacious (risk ratio 0.38; 95% CI, 0.17 to 0.85). In post-exposure prophylaxis trials, oseltamivir had an efficacy of 58% (95% CI, 15 to 79) and 84% in two trials of households. Zanamivir performed similarly. For treatment, the hazard ratios for time to alleviation of influenza-like illness symptoms were in favor of treatment : 1.20 (95% CI, 1.06 to 1.35) for oseltamivir and 1.24 (95% CI, 1.13 to 1.36) for zanamivir. Regarding lower respiratory tract complications, evidence suggests oseltamivir did not reduce influenza related complications (risk ratio 0.55; 95% CI, 0.22 to 1.35).

A 2015 meta-analysis evaluated the efficacy of oseltamivir treatment for influenza in adults.<sup>79</sup> Data from nine trials including 4,328 patients was used in the analysis. The analysis showed that oseltamivir in adults with influenza accelerates time to clinical symptom alleviation, reduces risk of lower respiratory tract complications, and admittance to hospital, but increases the occurrence of nausea and vomiting. In the analysis, time to alleviation of all symptoms was 21% shorter for oseltamivir versus placebo in the intention to treat infected population (time ratio 0.79, 95% CI 0.74-0.85; p<0.0001). The analysis also showed fewer lower respiratory tract complications requiring antibiotics more than 48 hours after randomization (risk ratio [RR] 0.56, 95% CI 0.42-0.75; p=0.0001) and also fewer admittances to hospital for any cause (RR 0.37, 95% CI 0.17-0.81; p=0.013) in the intention to

treat infected population. Regarding safety, oseltamivir increased the risk of nausea (RR 1.60, 95% CI 1.29-1.99;  $p < 0.0001$ ) and vomiting (RR 2.43, 95% CI 1.83-3.23;  $p < 0.0001$ ).

## Children

A 2009 systematic review evaluated the effects of the neuraminidase inhibitors in treatment of children ( $\leq 12$  years old) with seasonal influenza and prevention of transmission to children in households.<sup>80</sup> Published and unpublished data were considered. A total of four randomized controlled trials with 1,766 children evaluated treatment with oseltamivir or zanamivir in the community setting with confirmed or clinically suspected influenza. Three randomized trials with 863 children evaluated post-exposure prophylaxis (one trial for oseltamivir, two trials for zanamivir). The median time to resolution of symptoms or return to normal activities or both was reduced by 0.5 to 1.5 days, which was a significant finding in only two trials. A ten-day duration of post-exposure prophylaxis with zanamivir or oseltamivir resulted in an 8% (95% CI, 5 to 12) decrease in the incidence of symptomatic influenza. Based on only one trial, oseltamivir did not reduce asthma exacerbations and oseltamivir was not associated with a reduction in overall use of antibiotics (risk difference -0.3, 95% CI, -0.13 to 0.01). Zanamivir was well tolerated, but oseltamivir was associated with an increased risk of vomiting (0.05, 95% CI, 0.02 to 0.09, number needed to harm=20).

## SUMMARY

Vaccination is the primary method of preventing influenza infection.

Agents approved for influenza prevention and treatment include amantadine (Symmetrel), rimantadine (Flumadine), oseltamivir (Tamiflu), zanamivir (Relenza), and peramivir (Rapivab). The CDC currently does not recommend the use of amantadine or rimantadine for the treatment or prophylaxis of influenza A due to viral resistance.

The CDC recommends treatment of influenza in hospitalized patients, patients with severe, complicated, or progressive illness, or patients at higher risk with either oseltamivir, zanamivir, or peramivir (Rapivab). Treatment should be initiated as early as possible because studies show that treatment initiated early (e.g., within 48 hours of illness onset) is more likely to provide benefit.

Zanamivir uses a complex administration device for inhalation and should not be used in patients with pre-existing respiratory disorders. For the treatment of influenza B, either oseltamivir, zanamivir, or peramivir (Rapivab) are recommended.

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